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Strategies for improving outcomes in NSCLC: a look to the future

Stahel, Rolf ; Peters, Solange ; Baas, Paul ; Brambilla, Elisabeth ; Cappuzzo, Federico ; De Ruysscher, Dirk ; Eberhardt, Wilfried Ernst Erich ; Felip, Enriqueta ; Fennell, Dean ; Marchetti, Antonio ; Paz-Ares, Luis ; Adjei, Alex A

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Author: Rolf Stahel Solange Peters Paul Baas Elisabeth Brambilla Federico Cappuzzo Dirk De Ruysscher Wilfried Ernst Erich Eberhardt Enriqueta Felip Dean Fennell Antonio Marchetti Luis Paz-Ares Alex A. Adjei



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Strategies for improving outcomes in NSCLC – a look to the future

Rolf Stahel,¹ Solange Peters,² Paul Baas,³ Elisabeth Brambilla,⁴ Federico Cappuzzo,⁵ Dirk De Ruyscher,⁶ Wilfried Ernst Erich Eberhardt,⁷ Enriqueta Felip,⁸ Dean Fennell,⁹ Antonio Marchetti,¹⁰ Luis Paz-Ares,¹¹ Alex A. Adjei¹²

¹*Department of Oncology, University Hospital Zurich, Zurich, Switzerland*

²*Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland*

³*The Netherlands Cancer Institute Department of Thoracic Oncology and The Academic Medical Centre, Amsterdam, The Netherlands*

⁴*INSERM U823, Institut Albert Bonniot/UJF; CHU Albert Michallon Departement de Pathologie, Grenoble, France*

⁵*Istituto Toscano Tumori, Department of Medical Oncology, Livorno, Italy*

⁶*Radiation Oncology, University Hospitals Leuven/KU Leuven, Herestraat 49, 3000 Leuven, Belgium*

⁷*Department of Medical Oncology, West German Cancer Center, University of Duisburg, Essen, Germany*

⁸*Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain*

⁹*University of Leicester & Leicester University Hospitals, Leicester, UK*

¹⁰*Center of Predictive Molecular Medicine, Center of Excellence on Aging, University Foundation, Chieti, Italy*

¹¹*Instituto de Biomedicina de Sevilla, University Hospital Virgen del Rocío, Seville, Spain*

¹²*Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA*

Address for correspondence:

Professor Rolf Stahel

Department of Oncology, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland

Tel: +41 44 634 2871; Fax: +41 44 634 2872; Email: Rolf.stahel@usz.ch

Abstract

Advances in the management of non-small cell lung cancer (NSCLC) over the past 30 years have led to small increases in 5-year survival rates across Europe, though further improvements may require new treatment strategies. In order to improve efficiency and reduce the cost of development, future trials for new targeted agents in NSCLC should aim to recruit patients on the basis of tumour biology rather than clinical characteristics. However, identification of predictive biomarkers is required to maximise the benefits of new approaches and expedite the drug development process.

Nevertheless, the NSCLC landscape is changing rapidly, and recent improvements in our understanding of the molecular biology of the disease will help in the identification of novel targeted agents as well as assisting in the development of personalised strategies for the numerous small subsets of defined NSCLC. Progress in imaging and treatment delivery is also likely to improve outcomes for patients with the disease. This article outlines recent progress in the treatment of NSCLC, identifies current challenges and describes proposals for improving the future management of the disease. It is hoped that implementation of some of these strategies will go some way to improving the outlook for patients with NSCLC.

KEYWORDS: Biomarkers, Clinical trials, Lung cancer, Management, Molecular profiling, Outcomes, Pathogenesis, Treatment

Introduction

Despite advances in the understanding of tumour biology in recent years, lung cancer mortality in Europe has remained largely unchanged over the past three decades, underlying the need for new treatment strategies [1,2]. Earlier diagnosis is also important, since outcome is primarily related to stage at diagnosis, with 5-year survival rates being over 70% for those with stage I disease falling to less than 5% for stage IV. Further challenges for improving NSCLC outcome include integration of new advances in clinical, pathological and molecular aspects into the management of the condition, since the landscape is changing rapidly.

Molecular pathology of NSCLC

Four main histological types of lung cancer are recognised: squamous cell carcinoma, adenocarcinoma and large cell carcinoma – known collectively as NSCLC – and small cell lung cancer (SCLC) [3,4]. However, mixed histology also occurs, complicating diagnostic evaluation. Nevertheless, the use of molecular analytical techniques in recent years has improved histological typing in lung cancer, especially in adenocarcinoma [3,5,6], with immunohistological markers such as cytokeratins (e.g. CK5/6) or transcription factors (e.g. p63, TTF1) being used to assist in the identification of different lung cancer subtypes in small biopsies where differentiation is not obvious.

Recently, a new classification of lung adenocarcinomas has been proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society (Table 1) [7]. The revised classification recognises that histological distinctions can be made between different prognostic subtypes, and that genetic alterations and response to therapy can be suggested by tumour pathology. It should be noted that diagnosis is made primarily on the basis of fine needle core biopsy or bronchial biopsies, limiting the amount of tissue available

for identifying different genetic alterations. Alternative biopsy methods should be considered, therefore, if molecular testing is planned. An algorithm, employing a minimal set of markers, is recommended for the diagnosis of lung cancer subtype in order to maximise the tumour tissue available for selected driver mutation research [7,8]. The new classification has been validated in a number of studies worldwide, including Europe [9,10]; however, its acceptance has been variable and more data may be required before it can be used to select patients for biomarker testing. Nevertheless, as new data emerge, the revised classification is expected to improve prognostic assessment for patients with adenocarcinoma, allowing subtyping to be used to stratify patients for treatment [10,11]. Recent studies characterising genomic alterations in NSCLC will also highlight new potential targets for treatment of the condition [12,13].

Use of biomarkers in NSCLC and the application of next-generation sequencing

Predictive biomarkers are needed in NSCLC in order to maximise the benefits of new treatment strategies and expedite drug development. Ideally, biomarkers should be specific, adaptable for standard clinical use and present only in tumour tissue. A good understanding of the molecular biology of the target is also required for biomarker development due to the existence of multiple, inter-related signalling pathways. Biomarker studies are difficult to perform for a number of reasons, including regulatory issues and tumour heterogeneity, with markers for both poor and good prognosis being found in the same tumour [14,15]. Additionally, intellectual property rights for assays can be a barrier to the clinical implementation of biomarkers and may limit drug development for rare mutations (e.g. frequencies <1%). Consequently, for widespread clinical application, the development of inexpensive and reproducible assays in parallel with drug development (companion diagnostics) is required. Collaboration between centres is also needed in order to standardise biomarker analyses and limit false positive or negative outcomes.

A number of predictive biomarkers for NSCLC have already been introduced into clinical practice. The most well established of these are epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements, commonly in the form of the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) fusion oncogene [16]. *EGFR* activating mutations are detectable in around 10% of patients with NSCLC in Western Europe [17], the most common of which occur in exons 19–21 and confer sensitivity to the tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib [18]. T790M, another frequently found *EGFR* mutation, is associated with TKI resistance and is present in around 50% of patients treated with EGFR TKIs at disease progression [19,20]. Recent data suggest that this mutation may be present at baseline rather than developing *de novo* after therapy [21]. *EML4-ALK* rearrangements are found in 2–7% of NSCLCs [22], most commonly in adenocarcinoma tumours from young people (<65 years old) who are light smokers or who have never smoked [23,24]. Other biomarkers thought to be associated with addiction to oncogenic driver mutations and that are predictive of response to specific agents in NSCLC include BRAF, HER2, ROS1, FGFR1 and MET. KRAS is a driver mutation for which no specific targeted drug has yet been identified, and is thought to confer relative resistance to EGFR TKIs [25–32]. More evidence is required to validate biomarkers such as PIK3CA, ERCC1, MSH2, TS, BRCA1 and RRM1 [33,34].

Testing of adenocarcinomas for *EGFR* mutation and *ALK* rearrangement is now recommended in current guidelines and is undertaken routinely in many centres [35]. The only validated assay for detecting *ALK* rearrangement at present is fluorescence *in situ* hybridisation (FISH), though good results have recently been achieved using an immunohistochemistry assay, which may be more applicable to routine testing [36]. DNA mutational analysis is the preferred method to assess EGFR status [37–39]. As routine testing for increasing numbers of mutations is likely in the future, the quality and availability of tissue samples could well become an issue [40].

One area that has seen an explosion in research in recent years is next-generation sequencing (NGS), which has the ability to fully sequence large numbers of genes in a single test (genome-wide analysis) with high sensitivity and at relatively low cost [41,42]. The genes identified can then be validated by re-sequencing, which can be used to help identify patients for particular treatments. A further important application for NGS in the future is the detection of mutations in body fluids, circulating tumour cells (CTCs), plasma or sera, since the mutations may be highly correlated with the primary tumour [43]. Sampling at different time points using this method may help to identify mutations evolving after different lines of treatment. NGS has already been adopted in some centres and may be used in the future to develop companion diagnostic tests for new drugs [44]. NGS holds great promise for the future, though the technology is not yet being used to guide treatment in NSCLC. Problems associated with the uptake of NGS include the lack of central regulation and standardisation for the platforms used, the interpretation and validation of findings, reimbursement and the financial implications of identifying rare mutations.

Current treatment options and new developments for NSCLC in Europe

Current treatment for NSCLC in Europe is based primarily on European Society for Medical Oncology (ESMO) guidelines [35], and is selected according to molecular subtype, performance status (PS) and comorbidity. However, local adaptations to treatment selection occur due to differing reimbursement policies and access to drugs. Furthermore, drug costs for long-term treatment are likely to play an increasingly important role in the future, particularly in the case of maintenance treatment for metastatic disease.

The recommended first-line treatment for metastatic NSCLC is platinum-based chemotherapy for all patients with PS 0–2, with an EGFR TKI being given to those with tumours bearing an activating (sensitising) *EGFR* mutation [35,45]. For healthy patients with stage I–II NSCLC, lobectomy is the treatment of choice. Adjuvant cisplatin-based chemotherapy is recommended for patients with

stage II–III NSCLC after radical resection according to the 7th TNM (Tumour, Nodes, Metastasis) classification [46]. Current guidelines for patients with stage III disease recommend the use of chemotherapy and radiotherapy, either sequentially or (preferably) concurrently [46]. However, treatment for stage III NSCLC is particularly challenging due to patients' comorbidities and tumour heterogeneity. Although treatment approaches for stage III NSCLC differ considerably between regions and centres, neoadjuvant (chemo-)radiotherapy followed by surgery remains a standard option in selected patients with resectable stage IIIA NSCLC. New drug development and research into the optimum chemo-radiation strategies for locally advanced NSCLC is also problematic due to the fact that patients are potentially curable and may not be willing to enrol in clinical trials. Novel approaches currently being investigated in stage III NSCLC include immunomodulatory strategies, agents acting on the cell cycle (e.g. aurora kinase inhibitors) and novel cytostatics [47,48]. 'Window of opportunity' trials undertaken before chemotherapy or chemo-radiotherapy may be a useful means of testing new agents or strategies in this population. Such trials allow the efficacy of novel therapies to be investigated before the development of resistance arising from prior therapy [49]. Although this approach raises possible ethical concerns relating to the use of an agent of indeterminate efficacy when standard therapies are available, window trials, if carefully controlled, can provide valuable information on the activity of new treatments for NSCLC [49,50].

The use of radiotherapy in lung cancer has seen a number of advances in recent years, with kinetics as well as heterogeneity of tumours being taken into account [51–53]. Uptake of radionuclides can also vary within tumours due to differing vascularisation. This presents the possibility of targeting different parts of the tumour with varying amounts of radiation to deliver higher doses with less toxicity [54]. Further possible future developments in radiotherapy are the combination of radiotherapy with targeted agents [55], and the use of proton-based technology, since such delivery improves target volume distribution and is more lung-sparing than photon-based delivery. Imaging biomarkers such as fluorodeoxyglucose (FDG)-positron emission tomography (PET) are also likely to

be used increasingly in the future to predict an early response to radiotherapy, with changes in FDG uptake by the primary tumour found to be significantly predictive for 2-year survival in stage III NSCLC during the first week of (chemo-)radiotherapy [56].

Clinical challenges of drug resistance in advanced NSCLC

Although cytotoxics like cisplatin have been used in the treatment of NSCLC for several decades, the mechanism(s) underlying resistance to these agents are poorly understood. Nevertheless, a number of predictive biomarkers for resistance to cytotoxics are being investigated, including ERCC1 and RRM1. Data suggest that patients with low levels of RRM1 or ERCC1 expression may respond better to carboplatin/gemcitabine [57,58]. However, current data are not robust, particularly for ERCC1 due to the lack of specificity of current antibodies [59]; prospective validation is needed, therefore, before routine testing for ERCC1 or RRM1 can be recommended.

Mechanisms of resistance to TKIs include oncogene-dependent second-site mutations or gene amplification and oncogene-independent bypass tracks (Figure 1) [60]. Resistance also arises from tumour heterogeneity, since mutations are not found in every tumour cell and there could be outgrowth of subpopulations with rare mutations under treatment pressure, leading to acquired resistance [61]. In addition, resistance can occur as a result of pharmacokinetic factors due to decreases in drug levels, with differences occurring between patients; however, drug concentrations within tumours are not well understood.

The T790M mutation is one of the major mechanisms of resistance to erlotinib and gefitinib [62]. The use of irreversible pan-HER agents (e.g. neratinib, afatinib) to overcome T790M EGFR resistance has not been encouraging, with very low response rates being observed [63,64]. Specific EGFR T790M inhibitors are also in development, though there are no clinical data with these agents to date [65]. The lack of success with targeting this mutation thus far may be due to the fact that its

expression is not well understood, and this highlights the need for caution when identifying resistance genes since they may not be activated *in vivo*.

The optimum management for patients whose disease progresses after TKI therapy is unclear, and chemotherapy is the only approved systemic treatment at present. One strategy currently under investigation in this population is to continue TKI therapy beyond progression, using local treatment such as radiotherapy when needed, thus delaying a change in systemic therapy. Although there are no prospective data investigating TKI maintenance beyond progression, the results of retrospective studies suggest that this strategy may improve both response rate and survival [66,67].

A further approach for patients with TKI-resistant tumours is the combination of targeted agents. Indeed, the ongoing trial of cetuximab plus afatinib has demonstrated clinical benefit in 75% of patients with TKI-resistant NSCLC [68]. However, the use of a combination of targeted agents has been problematic to date due to toxicity. Consequently, the addition of a cytotoxic to a targeted agent may be a more promising strategy both in patients with TKI-resistant tumours [69] and upfront in untreated patients [70].

Novel targets for drug treatment in NSCLC

The biology of the different mutations in NSCLC is complex and validation of the various targets is challenging. Hundreds of new mutations have been identified in NSCLC in recent years, particularly non-hot spot mutations, which are present in 20–30% of NSCLC tumours, though establishing the relevance of these mutations is difficult. An improved understanding of these gene alterations is needed in order to assist in the identification of new therapeutic targets leading to improved clinical outcomes. This will require translational laboratory research to establish underlying oncogene addiction.

Despite the complexity of the molecular biology of NSCLC, a vast array of new targets for NSCLC drug treatments are being investigated (Table 2), including HER2 and HER3. Although HER2 receptor overexpression occurs in around 30% of NSCLCs, the results of trials with anti-HER2 agents have not been encouraging [71,72]. As phosphorylation of EGFR is frequently through HER3 [73], addition of an anti-HER3 drug to improve the efficacy of anti-EGFR agents has also been investigated, and trials to investigate this strategy are ongoing.

KRAS is a frequent mutation in lung cancer tumours that was previously thought to be un-druggable; however, recent studies suggest alternative ways of targeting this mutation. One such strategy involves inhibition of cyclin-dependent kinase 4 (CDK4), since KRAS appears to be dependent on this cell cycle progressing molecule in animal models [74]. Inhibition of MEK has also been investigated, with a progression-free survival (PFS) benefit being demonstrated for the MEK inhibitor, selumetinib, when used in combination with docetaxel in patients with KRAS mutant tumours [75]. The latter findings should be treated with caution, however, as the effects of this agent in KRAS wild-type or an unselected population is unknown. Nevertheless, recent preclinical data provide support for the combination of MEK and BCL-XL inhibition as a strategy for targeting KRAS [76]. Immunotherapeutic strategies are also being investigated, and encouraging results have been demonstrated for the anti-cytotoxic T-cell lymphocyte-4 monoclonal antibody, ipilimumab, when used in combination with paclitaxel and carboplatin as first-line therapy in patients with stage III NSCLC [77]. Blockade of programmed death-1 (PD-1), a co-inhibitory receptor expressed by activated T-cells, has also been examined as a strategy to overcome immune resistance and mediate tumour regression [78], though selection of the subpopulation of patients who will benefit from this strategy will be challenging.

There is a need for improved trial designs for the development of new targeted agents for NSCLC, particularly when targeting rare and infrequent mutations like DNA repair deficiencies, with studies including assessment of biomarkers and involving selected populations. Ideally, new drugs should be

investigated initially in the metastatic setting before earlier settings are studied, with development targeting the non-smoking population in the first instance to maximise response.

Provision of healthcare services and treatment challenges for patients with NSCLC in Europe

Improvements in the provision of oncology healthcare services in Europe are needed due to escalating drug costs and limited funds. While certain barriers to advances in healthcare provision exist in Europe (differences in language, local policies, medical approaches and funding), progress is being made, with a number of networks being set up to report on health status across the region. These networks (e.g. the European Oncology Thoracic Platform [ETOP], European Organization for the Research and Treatment of Cancer [EORTC] and the International Association for the Study of Lung Cancer [IASLC]) will play a key role in improving healthcare provision in oncology in the future, enabling collaboration between healthcare professionals and industry in order to improve outcomes [79,80]. Such collaborations are important, since the incidence of lung cancer and mortality rates differ widely across Europe [1,81].

The advent of novel targeted therapy for patients with NSCLC has resulted in clear progress in the treatment of this common malignancy in recent years, though challenges still remain (Table 3). In particular, optimum use of novel agents requires the identification of predictive markers to determine the patients who will derive the most benefit. New models for clinical trials in NSCLC are also required, as the results of many Phase III trials with targeted agents undertaken over the last decade have been negative, primarily due to the inclusion of unselected patients and limited understanding of tumour biology [71,82–84]. The poor efficacy observed in early trials with targeted agents may also be due to cross-stimulation of the targets of these agents, such that interference with a single pathway may not be sufficient [85]. Consequently, to improve cure rates, consideration

should be given to the combination of targeted agents, with multiple biopsies being collected to study tumour evolution over time.

In order to improve efficiency and reduce the cost of development, future trials for new targeted agents in NSCLC should aim to recruit patients on the basis of tumour biology rather than clinical characteristics. Indeed the benefit of this approach has already been established, with crizotinib receiving accelerated approval within 4 years following demonstration of considerable efficacy in a targeted (*ALK+*) population [86]. Nevertheless, involvement of networks such as ETOP may be needed so that trials can be undertaken in selected populations due to the number of patients required for screening. New surrogate endpoints (e.g. quality of life or PFS) are also needed for future trials due to the difficulty in demonstrating survival benefit.

Adjuvant platinum-based chemotherapy improves survival in completely resected early-stage NSCLC and is now standard treatment in this setting based on the results of phase III trials [87–90]. Nevertheless, the impact is limited and predictive markers are needed in order to better select the patients most likely to benefit from adjuvant treatment. Indeed, the value of this strategy has already been demonstrated in the IALT trial in which adjuvant cisplatin-based chemotherapy significantly prolonged survival among patients with completely resected NSCLC and ERCC1-negative tumours (hazard ratio [HR] 0.65; $p=0.002$), whereas no benefit was seen in ERCC1-positive patients (HR 1.14; $p=0.40$) [88]. Recently, however, this finding has been called into question due to the inability of currently available ERCC1 antibodies to detect the unique functional ERCC1 isoform [59]. Consequently, the usefulness of ERCC1 expression in guiding treatment for NSCLC patients is limited at present. Nevertheless, the results of several ongoing studies investigating tailored adjuvant therapy based on expression of other markers (e.g. EGFR mutations and thymidylate synthase) are eagerly awaited. Additionally, use of immunotherapy in the adjuvant setting is being evaluated in the MAGRIT (MAGE-A3 as Adjuvant, Non-Small Cell Lung Cancer Immunotherapy) trial. Gaining a

better understanding of the biology of targeted agents and obtaining long-term toxicity data before investigation in the adjuvant setting is also likely to improve the success of adjuvant trials.

Summary

Advances have been made in NSCLC management over the last three decades leading to small increases in 5-year survival rates across Europe (2–7%) [91–94], though further improvements are needed. However, advances in understanding of the molecular biology of the disease will help in the identification of novel targeted agents and development of personalised strategies for the numerous small subsets of defined NSCLC, with progress in imaging and treatment delivery also likely to improve outcomes. Furthermore, it is hoped that implementation of some of the strategies identified in this article will go some way to improving the outlook for patients with NSCLC.

Conflict of interest statement

Rolf Stahel has provided consultation, attended advisory boards and/or provided lectures for Astellas, Abbott Diagnostics, Amgen, AstraZeneca, Boehringer Ingelheim, BMS, Daiichi Sankyo, GSK, Hoffmann–La Roche, Eli Lilly, Merck Serono, Merrimack, Pfizer and Tesaro; Solange Peters has provided consultation, attended advisory boards and/or provided lectures for Astellas, Hoffmann–La Roche, Eli Lilly and Company, AstraZeneca, Pfizer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Merck Serono, Merrimack and Tesaro; Paul Baas has participated in advisory boards for Astellas, Merck Sharp & Dohme and Pfizer; Elisabeth Brambilla has participated the Roche Ventana Advisory Board; Federico Cappuzzo has participated in advisory boards and consultancy for Roche, Astellas, Pfizer and AstraZeneca; W.E.E. Eberhardt has received honoraria in the last 2 years for advisory board and speakers' bureaux from Eli Lilly, Roche, Pfizer, AstraZeneca, Boehringer Ingelheim, GSK, TEVA, Amgen, Pierre Fabre, and Novartis, and research support from Eli Lilly; Dean Fennell has participated in advisory boards for Synta, Boehringer Ingelheim, Astellas and Eli Lilly; Antonio Marchetti has

participated in advisory boards and consultancy for Roche, Astellas, Qiagen, AstraZeneca and Transgenomics. All other authors report no conflict of interest.

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Figure legend

Figure 1. Mechanisms of tyrosine kinase inhibitor-acquired resistance. Reproduced with permission from Lovly & Pao, 2012 [59].

ALK, anaplastic lymphoma kinase; pEGFR, phosphorylated epidermal growth factor receptor.

Table 1

Adenocarcinoma classification proposed by the IASLC/ATS/ERS. Reproduced with permission from Travis et al., 2011 [7].

!! Preinvasive lesions

- Atypical adenomatous hyperplasia
- Adenocarcinoma *in situ* (≤ 3 cm [formerly BAC])
 - Non-mucinous
 - Mucinous
 - Mixed mucinous/non-mucinous

!! Minimally invasive adenocarcinoma (≤ 3 cm lepidic predominant tumour with ≤ 5 mm invasion)

- Non-mucinous
- Mucinous
- Mixed mucinous/non-mucinous

!! Invasive adenocarcinoma

- Lepidic predominant (formerly non-mucinous BAC pattern, with >5 mm invasion)
- Acinar predominant
- Papillary predominant
- Micropapillary predominant
- Solid predominant with mucin production

!! Variants of invasive carcinoma

- Invasive mucinous adenocarcinoma (formerly mucinous BAC)
 - Colloid
 - Foetal (low and high grade)
 - Enteric
-

ATS, American Thoracic Society; BAC, bronchioloalveolar carcinoma; ERS, European Respiratory Society; IASLC, International Association for the Study of Lung Cancer.

Table 2

Novel targets for drug treatment in non-small cell lung cancer and agents in development.

Target	Agent	Company	Phase of development
EGFR	GA201	Roche	I
HER2	Afatinib (BIBW2992)	Boehringer Ingelheim	III
	PF-00299804	Pfizer	II
HER3	MM-121	Merrimack Pharmaceuticals	I/II
	U3-1287 (AMG888)	U3 Pharma/Amgen	I/II
IGF-1R	Figitumumab (CP-751,871)	Pfizer	III
	OSI-906	OSI Pharmaceuticals/Astellas	II
	R1507	Roche	II
	Cixutumumab (IMC-A12)	ImClone Systems	I/II
	AMG-479	Amgen	I/II
	XL-228	Exelixis	I
HGF	AMG102	Amgen	II
MET	MetMAb	Roche	II
	XL880	Exelixis	II
	Cabozantinib (XL184)	Exelixis	II
	ARQ-197	ArQule	I
PI3K	XL-147	Exelixis/Sanofi	I
	GDC-0941	Genentech	I
PI3K/mTOR	XL-765	Exelixis/Sanofi	I
AKT	MK-2206	Merck	I
PARP-1	Iniparib	BiPar/Sanofi Aventis	II/IIII
	Veliparib	Abbot	I/II
	Olaparib	AstraZeneca	
TRAIL	Mapatumumab	GSK	II
	Conatumumab	Amgen	II
	CS-1008	Daiichi Sankyo	II
	PRO95780	Genentech	II
	AMG655	Amgen	I/II
Hsp90	Ganetespib (STA-9090)	Synta Pharmaceuticals	II/III
	IPI-504	Infinity	II
CDK	PD0332991	Pfizer	II
	Seliciclib (CYC202)	Cyclacel	II
HDAC	Vorinostat	Pantheon	II

CDK, cyclin dependent kinase; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HGF, hepatocyte growth factor; Hsp90, heat-shock protein 90; IGF-1R, insulin-like growth factor 1 receptor; mTOR, mammalian target of rapamycin; PARP-1, poly(ADP-ribose)polymerase-1; PI3K, phosphatidylinositol 3-kinase; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand.

Table 3

Challenges in NSCLC and suggestions for addressing them.

Challenge	Proposal for addressing
Healthcare policies, medical approaches and funding vary across Europe, limiting advances in oncology healthcare provision	!! Oncology platforms (e.g. EORTC, ESMO, ETOP, EurocarePlatform, IASLC) to co-ordinate collaboration between healthcare professionals and industry to improve outcomes
Incidence of lung cancer varies considerably between countries in Europe	!! Collaboration between countries and centres through ETOP and other oncology platforms !! Improvements in patient education !! Implementation of free screening and smoking cessation programmes !! Use of customised therapies to improve outcomes !! Identification of enriched populations to improve clinical trial success
Quality of care differs between centres	!! Concentration of healthcare provision in specialist centres
Mortality rates from lung cancer have remained largely unchanged over the past 30 years	!! Development of new treatment strategies !! Implementation of strategies aimed at earlier diagnosis
Progress in drug development in NSCLC has been slow and the results of many Phase III trials of targeted agents over the past decade have been negative	!! Identification of predictive biomarkers of response !! Recruitment of patients on the basis of tumour biology !! Involvement of oncology platforms such as ETOP to co-ordinate screening !! Use of a combination of targeted agents to avoid cross-stimulation of signalling pathways
Survival benefits are difficult to demonstrate in clinical trials	!! Development of surrogate endpoints (e.g. PFS, quality of life)
The benefit of adjuvant trials in NSCLC is unclear	!! Improvement in identification of the patients most likely to benefit from adjuvant therapy !! Obtain better understanding of the biology of targeted agents before investigation in the adjuvant

	setting
	!! Obtain long-term toxicity data on novel agents before undertaking adjuvant trials
The subpopulations who will benefit from particular targeted therapies is uncertain	!! Identification of predictive biomarkers of response
Intellectual property rights can be a barrier to the clinical use of biomarkers and may limit drug development for rare mutations	!! Development of inexpensive biomarker assays in parallel with drug development !! Collaboration between centres to avoid use of multiple detection methods, improve reproducibility and avert false positives
The quality and availability of tissue samples may be a challenge for the future due to routine testing for increasing numbers of mutations	!! Centralise molecular diagnostics across the oncology community to reduce costs and improve quality control
Treatment for stage III NSCLC is challenging due to patient comorbidity and tumour heterogeneity	!! Development of novel treatment approaches including immunomodulatory strategies, cell cycle agents and novel cytostatics !! Use of 'window of opportunity' trials to test new agents or strategies
Resistance to TKIs develops in almost all patients and the optimum treatment for progression after TKI treatment is unclear	!! Prospective studies investigating the benefit of continuation of TKI treatment beyond progression !! Combination of targeted agents or addition of a cytotoxic agent to a targeted agent to delay/prevent resistance

EORTC, European Organisation for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; ETOP, European Thoracic Oncology Platform; IASLC, International Association for the Study of Lung Cancer NSCLC, non-small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Figure

